Difference between end tidal and arterial PCO_2

By Alex Yartsev - 16/02/2020
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This chapter is vaguely related to Section F12(ii) from the 2023 CICM Primary Syllabus, which expects the exam candidates to be able to *"describe the principles of capnography, including calibration, sources of errors and limitations"*. Though the syllabus document does not explicitly state that this gap between PaCO2 and EtCO2 is essential knowledge, its constant appearance in the exams suggests that it probably is. It has featured in three SAQs, each of them essentially identical:

- Question 3 from the second paper of 2018
- Question 21 from the first paper of 2017
- Question 9 from the first paper of 2009

Of these, the college answer to Question 21 was the laziest (*"Many candidates didn't distinguish between the different types of dead space. In general this topic was not well understood."*). The other two, however, were informative as to what was expected. Additionally, this topic has come up in the Part two exam papers, as Question 9.2 from the second paper of 2008, which at least listed some different causes for the gradient. As a result, the revision section from the Part Two exam has a brief entry on this topic, to help refresh the memories of senior trainees. Obviously, some occasional refreshing is called for, because none of the aforementioned SAQs had a pass rate higher than 30%.

In summary:

- Normal $PaCO_2$-$EtCO_2$ difference is 2-5 mmHg (Satoh et al, 2015)
- This is due to alveolar dead space, which is small in healthy adults
  - If there was no alveolar dead space, end-tidal CO_2 would be identical to alveolar CO_2
  - Alveoli which are ventilated but not perfused (i.e. alveolar dead space) contain a gas mixture which is identical to inspired gas
  - Thus, the addition of their content to expired gas dilutes the expired CO_2 concentration and decreases the end-tidal CO_2 value
  - Anatomical dead space does not contribute to the *end-tidal* CO_2 concentration because at the end of expiration all of the anatomical dead space volume has already emptied
  - Where ventilation is "perfect" (i.e. alveoli empty maximally) and dead space is minimal, end-tidal CO_2 may be lower than aterial CO_2

- Factors which increase the $PaCO_2$-$EtCO_2$ difference include:
  - **Changes in pulmonary perfusion**
    - Regional decreases in pulmonary perfusion
      - Pulmonary embolism
      - Fat embolism
      - Air embolism
    - Globally reduced pulmonary perfusion:
      - Pulmonary hypertension
      - Cardiac failure (RHF)
      - Cardiac arrest
      - Extreme hypovolaemia (eg. haemorrhagic shock)
      - Very high PEEP or positive inspiratory pressure
  - **Changes in ventilation**
    - Increased V/Q mismatch or increased alveolar dead space
      - High PEEP or positive airway pressure
    - High FiO2 ((causing increased VQ mismatch by improving the perfusion of poorly ventilated alveoli, which resembles shunt)
    - Oesophageal intubation
    - Very large shunt fraction (>30%)
  - **Measurement error**
    - Dilution of expired gas, eg. the presence of helium
    - The presence of nitrous oxide (N_2O may be misinterpreted as CO_2)
    - The use of an inline HME filter can reduce the end-tidal CO_2 concentration.
    - The timing of the measurement may be wrong: the measurement is only valid if it is truly end-tidal, and so any scenario where the measurement is taken before the end of expiration would produce a falsely depressed value.

This gap is very well known, and is clearly a favourite among examiners in all sorts of critical care fields. As such, there are many good articles and it is difficult to make one specific recommendation from among multiple good resources. One stand-out reference is Michael Donnelan's chapter for *Applied Technologies in Pulmonary Medicine* (2011), which is somehow paywalled by Karger by available for free via Google Books. Another excellent resource is *Capnography Outside the Operating Rooms* by Bhavani Shankar Kodali (2013). Kodali is in fact a prolific FOAM author and his website (capnography.com) is an absolute goldmine of carefully referenced information, in essence a textbook on capnography for those unwilling or unable to pay full price for *Capnography* by Gravenstein et al (2011).

The influence of dead space on the $PaCO_2$-$EtCO_2$ gap

The college answer to Question 9 from the first paper of 2009 suggests we all go look at Power & Kam's *"Physiology for the Anaesthetist"* where apparently there is *"an excellent graph... which helps understand alveolar dead space"*. Back in those days, the college was somewhat undersubscribed with trainees, making them a valuable resource worth investing in; as such the examiner's comments are even furnished with a page reference to the aforementioned graph, something unthinkable in the modern era of disposable multitudes. Thus, it is possible to track down the aforementioned *excellent graph* and reproduce it here with no permission whatsoever (this version comes from the 3rd edition of the textbook, p.89):

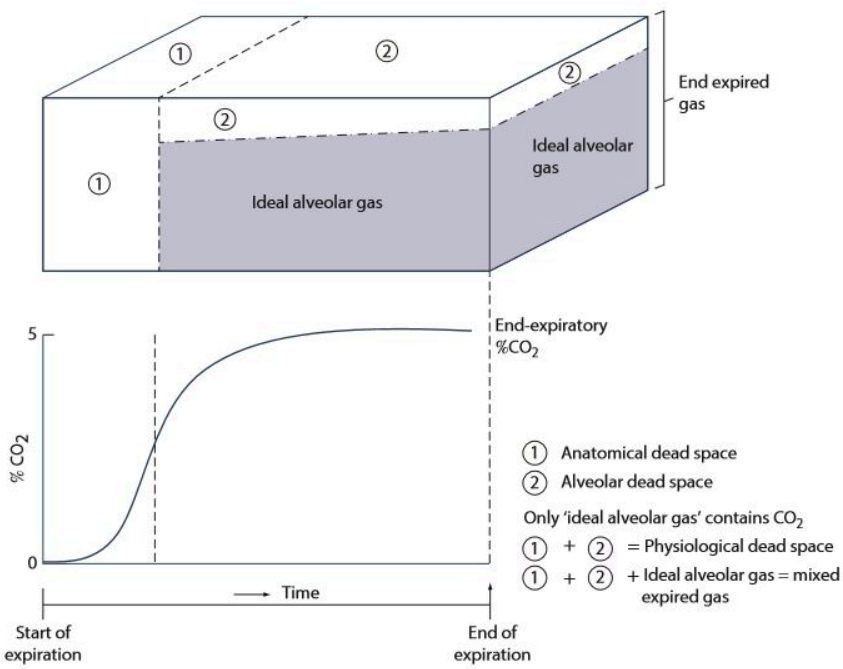


Figure 3.12 Components of an expired tidal volume.

Without going into an excess of detail (again), it will suffice to say that:

- If all of the expired gas volume originated in the alveoli, and all the alveoli were capable of ideal gas exchange (V/Q =1.0) then the arterial and expired PCO_2 would be exactly the same.
- However, this is clearly not the case:
    - Some of the expired volume originates from the conducting airways, and did not participate in gas exchange (this is the anatomical dead space)
    - Some of the expired volume originated from alveoli the gas exchange characteristics of which were not ideal (V/Q ≠1.0):

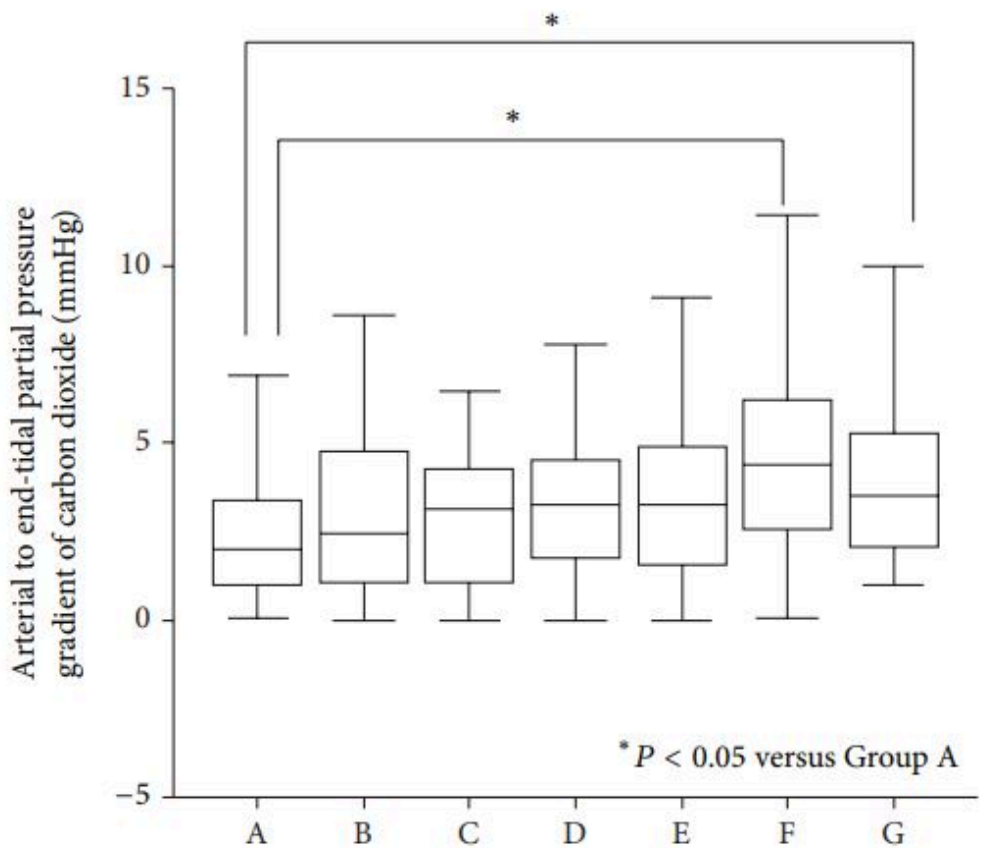
    - Of these, the alveoli affected by shunt would not count, as they were not ventilated and would therefore produce no expired gas. However, they also do not exchange CO_2, and would therefore increase the arterial CO_2 partial pressure, contributing to the total $PaCO_2$-$EtCO_2$ gap.
    - Alveoli affected by V/Q scatter (V/Q less than 1.0, but higher than 0) would not contribute to the total $PaCO_2$-$EtCO_2$ gap, as the expired gas coming out of them would resemble gas coming out of "ideal" alveoli.
    - Alveoli with a V/Q higher than 1.0 (but not an infinitely high V/Q) contribute to the $PaCO_2$-$EtCO_2$ gap by producing expired gas which is poor in CO_2, as there is way too much ventilation and the alveolar CO_2 ends up being diluted.
    - Alveoli with an infinitely high V/Q (i.e. alveoli which receive no perfusion at all) comprise the alveolar dead space, and contribute to the $PaCO_2$-$EtCO_2$ gap by producing expired gas which is indistinguishable from inspired gas, just like the conducting airways.
- Thus, the expired gas volume consists of a gas mixture from multiple compartments, of which only one (alveolar gas) has the same PCO_2 as arterial blood)
- Ergo, the total concentration of CO_2 in expired gas will always be lower than the arterial PCO_2.

So, basically, it's all to do with dead space. Alveolar dead space in particular is what affects the *end-tidal* CO_2 measurement, which is taken at the end of expiration. By that stage, anatomical dead space has completely emptied, and is no longer contributing to the total expired CO_2 value. One might correctly say that the anatomical dead space contributes to expired capno*graphy*, but not to end-tidal capno*metry,* as it affects the shape of the early capnography curve. The college felt strongly enough about this distinction to complain that *"many incorrectly attributed anatomical dead space as a contributor to the $PaCO_2$-$ETCO_2$ gradient"* in their answer to Question 3 from the second paper of 2018. Interestingly, though dead space is the major reason for the $PaCO_2$-$EtCO_2$ gap, according to the examiners *"discussion of the various types of dead space did not score marks"*.

Normal difference between $PaCO_2$ and $EtCO_2$

From the above, it follows that there is some normal value for the $PaCO_2$-$EtCO_2$ gap, which would correlate to the volume of alveolar dead space (normally, a very small volume in healthy adults). Most textbooks give a range of 2-5 mmHg, usually without a reference. When a reference is available, they usually give Nunn & Hill (1960), who actually measured a mean value of 4.6 mmHg (S.D. ± 2.5)

For some more detailed empirical data, Satoh et al (2015) measured this gap in a series of patients, all anaesthetised and supine, and of different ages. The authors found values of 2.4-4.3 mmHg, which was apparently *"similar to the gradient of values previously reported for other clinical situations"*. The difference increases slightly with age, which the authors attributed to age-related decrease in FRC and increase in alveolar dead space. The difference was not massive: in the original image below (Satoh et al, 2015, Figure 1) groups A to G are decades of age, starting with age 16. As one can see, there was barely 1-2mmHg difference between the groups, and all groups up to the age of 76 had individuals with a 0mmHg gap (i.e. no alveolar dead space whatsoever).



Causes of an increased difference between $PaCO_2$ and $EtCO_2$

There are multiple possible reasons for an increase in the normally small difference between. These generally fall into three major categories. Either something happened to the lung's perfusion, or something happened to the ventilation of the perfused alveoli, or there is some problem with the way the measurement is being performed.

- **Pulmonary perfusion**
  - Regional decreases in pulmonary perfusion
    - Pulmonary embolism
    - Fat embolism
    - Air embolism
  - Globally reduced pulmonary perfusion:
    - Pulmonary hypertension
    - Cardiac failure (RHF)
    - Cardiac arrest
    - Extreme hypovolaemia (eg. haemorrhagic shock)
    - Very high PEEP or positive inspiratory pressure
- **Ventilation**
  - Increased V/Q mismatch due to high PEEP
  - Increased alveolar dead space
  - High FiO2 (causing increased VQ mismatch by improving the perfusion of poorly ventilated alveoli, which resembles shunt)
  - Oesophageal intubation
- **Measurement error**
  - The presence of helium can cause the EtCO2 measurement to be incorrectly elevated in some capnometers (i.e. those which use a reporting algorithm that assumes that the only gases present in the sample are those that the device is capable of measuring)
  - The presence of nitrous oxide can confuse some capnograph devices, and the N_2O may be misinterpreted as CO_2
  - The use of an inline HME filter can reduce the end-tidal CO_2 concentration.

- The timing of the measurement may be wrong: the measurement is only valid if it is truly end-tidal, and so any scenario where the measurement is taken before the end of expiration would produce a falsely depressed value.

Increased VQ mismatch due to high FiO_2

High FiO_2 reverses the perfectly reasonable and adaptive strategy of vasoconstriction and redistribution of blood flow away from poorly ventilated emphysematous lung units in patients with COPD. Lung units without much ventilation eventually develop hypoxia on room air and become definctioned by hypoxic pulmonary vasoconstriction so that more of the blood flow can be distributed to the "good" lung (one of the mechanisms underlying chronic pulmonary hypertension in COPD). Ideally, all those pointless wasteland alveoli should just remain dead space, but with high FiO_2 their blood flow improves, and they become a nuisance by trying to participate in gas exchange. Now they demand blood flow, and distract the normal compensatory mechanisms of the pulmonary circulation, reducing the total blood flow going to "good" units, which lowers the total gas exchange capacity of the system - because nothing has magically improved their poor ventilation. The result is that the total amount of CO_2 eliminated by the system is reduced, and therefore the arterial CO_2 is increased, widening the $PaCO_2$-$EtCO_2$ difference. One might reflexively describe this as shunt, because these lung units receive blood but no gas, just like collapsed or consolidated alveoli; but it would be impossible to keep a straight face in doing so, because the definition of shunt is "V/Q ratio = 0", i.e. no ventilation whatsoever, and obviously *some* oxygen gas needs to have wafted into there to cause the mismatch.

Causes of a *negative* $PaCO_2$ - $EtCO_2$ gap

Yes, it is also possible to have a negative $PaCO_2$ - $EtCO_2$ gap, i.e. scenarios where the arterial CO_2 is actually *lowe*r than the end-tidal, leading to confusion and bewilderment. Never fear: this is, in fact, what is *supposed* to occur, if you think about it carefully. Consider: the blood arriving to the lungs contains more CO_2 than the blood leaving the lungs (because respiratory gas exchange do be like that), and it would be logical to expect arterial blood to be CO_2-depleted. In other words, there should be an arteriovenous CO_2 gradient, and in fact that is what

you usually see, with a difference of around 6mmHg on average. Alveolar CO_2 is a bit unpredictable but generally supposed to be in equilibrium with end-pulmonary-capillary blood (which is basically the same as arterial blood, somewhere around 40 mmHg). However, because of the extremely rapid equlibration of CO_2 across the capillary distance, alveolar CO_2 can sometimes be more representative of *mixed venous blood*, which has a PvCO2 of 46mmHg or so. This can occur in several common scenarios:

- **Where there is a large cyclical change in alveolar CO_2 over the course of a breath:** For example, where the FRC is small - such as in pregnant women, obese patients and those who have just come off cardiopulmonary bypass. With so much of the cardiac output directed into the reduced lung volume by the helpful effects of hypoxic vasoconstriction, the flow through pulmonary capillaries enriches the alveolar CO_2 by continuously adding mixed venous blood. Also, with the pulmonary circulation adding CO_2 to a diminishing lung volume, that CO_2 will obviously get concentrated in those alveoli still remaining open towards the end of expiration. The pulmonary capillary CO_2 will also increase there, but because these capillaries are few in number, they will contribute little to the overall $PaCO_2$ which you sample from the radial artery (which is a mixed-together average $PaCO_2$ value).
- **High VT and low resp rates:** Where the respiratory rate is very low, and the tidal volumes are very large, deeper, slower alveoli are able to share their gas with the capnometer, whereas previously that gas would have remained in the airway. Also, deeper breaths can result in the recruitment of dependent alveoli which have low V/Q ratios, resulting in the evacuation of more CO_2-rich gas (Fletcher et al, 1984).
- **During strenuous exercise,** where there is greatly increased CO_2 production and minute ventilation, the same phenomenon is apparently seen (large variation in CO_2 over the course of a breath). The example is somewhat artificial, as performance athletes aren't usually in the ICU having their $EtCO_2$ measured while they're doing a sport, but theoretically anything that greatly increases the metabolic rate could produce this phenomenon, eg. anaesthetists may witness this when a patient develops malignant hyperthermia (Lin et al, 2014).
- **Wherever there is rebreathing of expired CO_2** the end-tidal CO_2 may end up higher than the arterial CO_2, at least initially.

- **Wherever there is some sort of inadvertant addition of CO_2** to the expired gas mixture - eg. intestinal CO_2 used for insufflation, escaping following gastroscopy, or laparoscopic CO_2, or thoracoscopic CO_2, etc (Biles et al, 1994).
- **Where a Phase IV exists in the end tidal CO_2** - this happens because small airways in the more compliant regions of the lung close, and only poorly compliant alveoli continue to exhale their CO_2-rich gas. Without anatomical dead space gas or gas from "better" alveoli to dilute it, this alveolar mixture is more representative of mixed venous CO_2.
- **Because the ABG is a mixed sample:** remember that arterial CO_2, same as alveolar CO_2, is actually *cyclical*, in the sense that it varies in time with the respiratory cycle and the cardiac cycle. However, when you aspirate the sample from the artery, the cyclicality is lost: the sample mixes and the CO_2 content is homogenised. The highest part of the cycle (more representative of mixed venous CO_2) may therefore be higher than the average of the aspirated sample.

Previous chapter: End-tidal capnometry

Next chapter: Measurement of oxygen tension by electrolysis of dissolved oxygen

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